REMARKS

Applicant respectfully requests entrance of the present Amendment. Claims 37-45 are pending; Claims 38-45 have been withdrawn from consideration; and Claim 37 is under examination, and has been rejected. Claim status identifiers have newly been added to claims 38-45 to indicate they are "withdrawn." Additional claim amendments have been made to Claims 37 and 40 as follows. Claim 37 has been amended to replace the phrase "and pharmaceutically acceptable salts thereof", with the phrase "or a pharmaceutically acceptable salt thereof." Exemplary support for this amendment is found at specification page 19, lines 25-26; page 63, line 10 through page 67, line 17; and original claim 1, specification page 135, line 22. Claim 40 has been amended to add the word "or" for clarification purposes only. Applicant submits that no new matter has been added by this Amendment.

I. Rejection under 35 U.S.C. §103

Claim 37 is rejected under 35 U.S.C. §103(a) as being unpatentable over Parrish et al. (i.e., WO03/028731). The Examiner asserts that one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the compounds encompassed by formula (I) of Parrish et al., including 5-(3-fluorophenyl)-3-ureidothiophene-2-carboxylic acid (S)-piperidin-3-ylamide (i.e., the compound of claim 37), because the compound of claim 37 is generically encompassed by formula (I) of Parrish et al., and Parrish et al. teaches the synthesis of such compounds as CHK1 kinase inhibitors. More specifically, the Examiner states:

> "[…] Parrish et al. teach compounds of formula (I): […] wherein R1 is H, R2 is C(O)NHR5 with R5 being a C0alkyl heterocyclyl; R3 is H and R4 is an aryl optionally substituted by A wherein A is a halogen (see pg. 2, compound of formula (I) and pg. 3). […] Parrish et al. do not specifically teach the compound, 5-(3-fluorophenyl)-3-ureidothiophene-2-carboxylic acid (S)-piperidin-3-ylamide. […] Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the compounds encompassed by formula (I) of Parish including 5-(3-fluorophenyl)-3-ureidothiophene-2-carboxylic acid (S)-piperidin-3-ylamide given that Parrish et al. teach synthesis of such compounds as CHK1 kinase inhibitors. Given the teachings of Parrish et al., one of ordinary skill would have been motivated to utilize the compound of formula (I) of Parrish including 5-(3-fluorophenyl)-3-ureidothiophene-2-carboxylic acid (S)-piperidin-3-ylamide with the reasonable expectation that such compounds are effective in inhibiting CHK1 kinase and effective

> in treating hyperproliferative diseases." (*compound structure of Parrish et al. formula (I) eliminated by Applicant*).

Applicant respectfully traverses and submits that the Examiner has not established a *prima facie* case of obviousness for the reasons set forth below. More particularly, the standard set forth for chemical compounds is:

> "Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been **[1]** motivated to select and then **[2]** to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old." *Daiichi Sankyo Co., Ltd. v. Matrix Laboratories Ltd.,* 619 F.3d 1346 (Fed. Cir. 2010) (citing to *Eisai, 533 F.3d at 1357*; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007))*. (*"[1]" and "[2]" added for emphasis by Applicant*).

Applicant respectfully submits that the Examiner has failed to address each of the above requirements (i.e., that a medicinal chemist of ordinary skill would have been **[1]** motivated to select and then **[2]** to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old), and therefore a *prima facie* case of obviousness has not been made. Applicant now addresses each requirement in turn.

(a) Selection of a Lead Compound

The Examiner failed to recite a finding as to why one of ordinary skill in the art would have selected any compound in the Parrish et al. as a lead. Rather, the Examiner merely cited to Parrish et al. stating that it:

> "teach[es] compounds of formula (I): [...] wherein R1 is H, R2 is C(O)NHR5 with R5 being a C0alkyl heterocyclyl; R3 is H and R4 is an aryl optionally substituted by A wherein A is a halogen." (see Office Action at page 4),

which appears to be a means to show that Applicants' compounds are structurally similar to those found in Parrish et al. However, selecting a lead solely based on structural similarity "runs contrary to our case law." (See *Daiichi* at 1354). A plethora of support for this is found throughout case law. For example:

The Federal Circuit in *Procter & Gamble* states:

> "An obviousness argument based on structural similarity between claimed and prior art compounds 'clearly depends on a preliminary finding that

> one of ordinary skill in the art would have selected [the prior art compound] as a lead compound.'" *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc. 566 F.3d 989,994 (Fed. Cir. 2009)* (citing to *Takeda,* 492 F.3d at 1359; see also *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

The Federal Circuit in *Daiichi* states:

> In *Takeda*, [the Federal Circuit] upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound, [...] as the lead compound in light of other compounds with more favorable characteristics. [...] [the Federal Circuit] reached the same result in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals."* (See *Daiichi* at 1354).

The Federal Circuit in *Daiichi* also rejected the use of "undisputedly the closest prior art" compound as a lead. Rather, "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds." (See *Daiichi* at page 1354 (citing to *Eli Lilly,* 471 F.3d at 1377-79)) was the governing standard. Indeed, "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds" and "potent and promising activity in the prior art trumps mere structural relationships." (See *Daiichi* at page 1354).

Accordingly, the Examiner failed to recite why one of ordinary skill in the art would have selected any compound found in Parrish et al. as a lead compound.

(b) Motivation to Modify

The Examiner failed to set forth specific reason(s) why one of ordinary skill in the art would have been motivated to modify any of the compounds in Parrish et al. to arrive at the presently claimed compound.

The Examiner appears to have used structural similarity and/or a genus-species relationship as a *per se* rule for finding a *prima facie* case of obviousness without performing the requisite analysis discussed above. This is improper not only pursuant to current case law, but also according to the U.S.P.T.O.'s updated examination guidelines recently published in the Federal Register, which states:

> When considering obviousness, Office personnel are cautioned against treating any line of reasoning as a *per se* rule [...] such rationales should not be treated as *per se* rules, but rather must be explained and shown to apply to the facts at hand [...] Simply stating the principle (*e.g.,* ''art recognized equivalent," "structural similarity'') without providing an

> explanation of its applicability to the facts of the case at hand is generally not sufficient to establish a *prima facie* case of obviousness. (see "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex," Fed. Reg., Vol. 75, No. 169, pp. 53643 and 53645) (hereinafter referred to as the "*Examination Guidelines*").

The Examination Guidelines further state:

> Although the *KSR* approach is flexible with regard to the line of reasoning to be applied [...] ''The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.'' [...] When setting forth a rejection, Office personnel are to continue to make appropriate findings of fact as explained in MPEP §§ 2141 and 2143, and must provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention. This requirement for explanation remains even in situations in which Office personnel may properly rely on intangible realities such as common sense and ordinary ingenuity. (See Examination Guidelines, emphasis added by Applicant).

Here, the Examiner failed to set forth specific reason(s) why one of ordinary skill in the art would have been motivated to modify any of the compounds in Parrish et al. to arrive at the presently claimed compounds.

In conclusion, the Examiner has not set forth a *prima facie* case of obviousness, as neither of the two-prongs recited in *Daiichi* have been met (i.e., that a medicinal chemist of ordinary skill would have been **[1]** motivated to select and then **[2]** to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old).

Thus, Applicant submits that claim 37 is not obvious over Parrish et al. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of this claim under 35 U.S.C. § 103(a).

II. Request for Rejoinder

Applicant submits that claim 37 is allowable. Consistent with MPEP §821.04(b), the nonelected/withdrawn subject matter of claims 38-45 in their present form are commensurate in scope with the elected subject matter of compound claim 37. Thus, corresponding claims

38-45 are properly eligible for rejoinder. Therefore, Applicant respectfully requests that examination on the merits proceed accordingly.

III. IDS Reference

The Examiner considered the IDSs submitted October 23, 2008, and June 22, 2010, and, according to the notation placed at the end of each page (i.e., "All references considered except where lined through. /S.J.L."), has initialed all references. However, because there is a separate notation next to the 2nd reference on page 3 of the October 23, 2008, IDS (entitled "AstraZeneca PLC. Novel thiophenecarboxaminde IKK-2 inhibitors. Expert Opinion on Therapeutic Patents (2005), 15(3), 343-347") stating "Not Provided," it is unclear whether that reference was indeed considered. For the purposes of clarity, Applicant resubmits this single reference in a Supplemental IDS for the Examiner's consideration. If, however, the Examiner has previously considered this reference, then Applicant respectfully requests that the Examiner separately acknowledge this by initialing the Supplemental IDS submitted herewith.

IV. Final Remarks

Applicant thanks the Examiner for careful consideration of this case and invites the Examiner to contact the undersigned, Julie Anne Knight, at (781) 839-4002 with any questions pertaining to the above-identified application in order to expedite prosecution of this case.

A payment in the amount of $1,110.00 covering the fee set forth in 37 C.F.R. §1.136 is being paid via the USPTO's electronic filing system's credit card payment option. Applicant believes that no additional fee is required. However, the Commissioner is hereby authorized to charge any fees which should have been filed herewith (that are necessary to keep the present application pending and/or protect the filing date of this application) to our Deposit Account No. 50-3231 referencing Attorney Docket No. 101367-1P US/O. No authorization is given to charge monies for optional fees.

Respectfully submitted,

/Julie Anne Knight/

Name: Julie Anne Knight
Dated: **April 27, 2011**
Reg. No.: 48,867
Phone No.: (781) 839-4002
Global Intellectual Property, Patents
AstraZeneca R&D Boston
35, Gatehouse Drive
Waltham, MA 02451